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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,945	05/02/2001	Neil P. Desai	ABI1460-3 (071243-1317)	6174

30542 7590 04/21/2004

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EXAMINER	
GOLLAMUDI, SHARMILA S	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,945	DESAI ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

Receipt of Request for Continued Examination received on February 11, 2004 and the Amendment to the Specification received on November 18, 2003 is acknowledged. Claims **1-30** are pending in this application.

Priority

Receipt of Petition to Accept an Unintentionally Delayed Domestic Priority Claim under 37 CFR 1.78(a)(3) is acknowledged.

However, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The claim to priority in Amendment to the Specification received on November 13, 2003 is improper and priority has not been granted. It should be first noted that applicant has incorrectly stated that application 09/446,783 was filed June 26, 1998. However, the correct date of filing is May 16, 2000. The instant application claims priority to US application 09/446,783 filed on May 16, 2000, which claims priority to PCT/US98/13272. This US PCT only claims priority to US application 08/926,155, filed in September 9, 1997 and claims priority to 60/051, 021, filed in June 27, 1997. Thus, the chain of priority of the international application is broken at June 27, 1997. An international application can only claim priority back one year before the filing of the international application. See MPEP 1878, Item 2, thus breaking the chain of priority thorough the international application.

Thus, the only valid claim to priority in the Amendment filed on November 18, 2003 is the statement, "This application is ....a 371 of PCT/US98/13272, filed 26 June 1998, which is a continuation-in-part of U.S. Patent Application Serial No. 08/926,155, filed 9 September 1997, now U.S. Patent No. 6,096,331." Therefore, the priority date of the claimed subject matter is established as September 9, 1997.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 18-20, and 23-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of treating of hyperplasia by administering antineoplastics, antiproliferatives, and angiogenesis inhibitors coated with a protein, does not reasonably provide enablement for the method of treating of hyperplasia by administering a drug coated by a protein or a composition for treating hyperplasia containing a drug coated with a protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in the view of the Wands factors (MPEP 2164.01 (a)). These include the nature of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, and state of the prior art. All of the

Wands factors have been considered with the regard to the instant claims, with the most relevant discussed below.

Nature of the Invention: Rejected claims 1-8 are drawn to a method of treating hyperplasia by administering a composition containing a drug coated with a protein. Rejected claims 9-16 are drawn to a method for reducing neointimal hyperplasia by administering a composition containing a drug coated with a protein. Claims 18-20 and claims 23-25 are drawn to a composition for the treatment of hyperplasia that contains a drug and protein. Claims 25-28 are drawn to a composition for reducing neointimal hyperplasia that contains a drug coated with a protein. The nature of the invention is encompasses administering **any** drug with a protein to treat hyperplasia.

Breath of the claims: The complex nature of the claims is greatly exacerbated by the breath of the claims. The claims encompass administering any type of drug such as antibiotics, with any type of protein to treat hyperplasia.

Guidance of the Specification: The guidance by the specification speaks on how the administer antineoplastics, antiproliferatives, immunosuppressives, and angiogenesis inhibitors to inhibit proliferation and migration of cells. Further, the specification speaks on to administer other forms of drugs with a protein to prevent toxicity. However, guidance is not provided on how to actually enable one to utilize any drug such as a simple over-the-counter medication to treat hyperplasia, a complex disease that involves the abnormal multiplication and growth of cells.

Working Examples: All of the working examples provided by the specification are directed towards the treatment of hyperplasia utilizing paclitaxel and the reduced

toxicity of paclitaxel utilizing a protein as a stabilizer. However, the examples to not enable one to utilize any generic drug to treat hyperplasia

Predictability of the Art: The lack of significant guidance from the specification or the prior art with regard to the treatment of hyperplasia utilizing any type of drug makes practicing this scope of the invention unpredictable.

The Amount of experimentation Necessary: Due to the vastness of compounds classified as drugs, an artisan of ordinary skill would undergo undue experimentation in deducing which drugs actually treat hyperplasia within applicant's scope.

The State of the Art: The state of the art recognizes the use of antineoplastic or antiproliferative drugs to treat hyperplasia. However, the state of the art does not recognize the use of other drugs, such as antibiotics known in the art to treat bacterial infections or simple over the counter cold medications known to alleviate cold symptoms, in treating hyperplasia.

In view of the above considerations, the instant claims are rejected over lack of enablement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18-20 and 23-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Mathiowitz et al (5,271,961).

Mathiowitz et al disclose protein microspheres containing insulin. See examples. Example 6 discloses an intravenous composition. The microspheres have a diameter between nanometers and micrometers, 0.01 micron to less than 100 microns. See column 3, lines 55-60. The compound may be dispersed in the protein solution as particles. See column 8, lines 1-2.

Note that the rejected claims recite intended use, which is not given patentable weight unless it provides a structural limitation.

Claims 18-21 and 23-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Grinstaff et al (5,498,421).

Grinstaff et al disclose encasing a water-insoluble biologically active agent in a polymeric shell (microparticles and nanoparticles) for in vivo delivery. See abstract and column 1, lines 60-64. The delivery of the actives in the form of particles allows for targeting organs for treatment, increased stability of the insoluble active agent compared to simple emulsions, emulsifier-free system, a solubilizer-free system wherein allergic reactions are reduced, and the use of small doses. See column 7, lines 15-26. Grinstaff disclose proteins as suitable biocompatible materials for the formation of the polymeric shell. See column 8, lines 36-68. The active agents that may be incorporated into the polymeric shell are taxols and camptothecin. See column 14, lines 1-6. Example 6 demonstrates the reduced toxicity of the drugs in the polymeric shells.

*Note the rejected claims recite intended use. For instance, the recitation a composition "for reducing hyperplasia associated with vascular interventional procedure" does not hold patentable weight unless the intended use provides a structural limitation.

Response to Arguments

Applicant argues that Grinstaff et al does not constitute prior art since instant application claims priority to the same priority date as Grinstaff et al.

Applicant's arguments have been fully considered but they are not persuasive. As discussed above, the priority date of the claimed subject matter is established as September 9, 1997 and Grinstaff et al has a filing date of February 22, 1994 and a priority date of March 26, 1993. Therefore, US patent 5,498,421 constitutes prior art.

Claims 1-4, 6-13, 15, 17-21, and 23-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Kunz et al (5,733,925).

Kunz et al disclose methods for inhibiting stenosis following vascular trauma or disease, cancer, diseases resulting from hyperactivity or hyperplasia of somatic cells. Example 7 discloses smooth muscle proliferation in the neointima. Kunz teaches direct or targeted delivery of therapeutic agents to vascular smooth muscle cells. See column 1, lines 15-35. Inhibiting stenosis following angioplasty is contemplated. See column 3, lines 54-62. The dosage forms are preferably in biodegradable microparticulates or nanoparticulates wherein the particles are formed of a polymer-containing matrix that biodegrades. Kunz et al teach conjugating the drug with a binding protein to target the cells and reduce toxicity. Example 7 notes the toxicity of a free drug versus a

conjugated drug. See column 14, lines 25-33. Kunz et al disclose that the direct sustained release dosage form-binding protein or peptide conjugations may disrupt binding protein/peptide target cell recognition. Therefore, ligand sandwich attachment techniques are utilized. Such a technique involves the formation of a primary peptide or protein shell using a protein that does not bind to the target cell population. The binding protein/peptide is then bound to the primary peptide or protein shell to provide a particulate with functional binding protein/peptide. For example, the poly-lactic/glycolic acid particulates are reacted with avidin or streptavidin to form protein-coated particulates. Additionally, the binding protein/peptide may be partially entrapped in the particulate polymeric matrix upon formation of the particulate. See column 25, line 20 to column 26, line 40. Therapeutic agents such as taxol or analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Taxol is taken into the cell and stabilizes the cell from further dividing. See column 4, lines 40-45 and column 13, lines 24-27. Examples of dosages include .01 to 10 mg/kg per day. For prevention of restenosis following angioplasty or an intervention that contributes to the acute proliferation of smooth muscle cells, a pre-loading dose is given prior to or at the time of intervention with smaller chronic doses given two or three weeks after intervention. For example, a single dose may be administered about 24 hours prior to intervention, while multiple preloading doses may be administered daily for several days prior to intervention. See column 29, lines 10-15. Delivery of the active agents may be intravenous, intra-arterial (stents), or local delivery. See column 30, lines 56-65 and examples for stent deployment.

Response to Arguments

Applicant argues the obviousness rejection based on Kunz et al in view of Grinstaff et al.

However, upon further review and consideration of Kunz et al, it is the examiner's position that Kunz et al anticipates the instant claims. Therefore, the arguments are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5, 14, 16, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunz et al (5,733,925).

Kunz et al disclose methods for inhibiting stenosis following vascular trauma or disease, cancer, diseases resulting from hyperactivity or hyperplasia of somatic cells. Example 7 discloses smooth muscle proliferation in the neointima. Kunz teaches direct

or targeted delivery of therapeutic agents to vascular smooth muscle cells. See column 1, lines 15-35. Inhibiting stenosis following angioplasty is contemplated. See column 3, lines 54-62. The dosage forms are preferably in biodegradable microparticulates or nanoparticulates wherein the particles are formed of a polymer-containing matrix that biodegrades. Kunz et al teach conjugating the drug with a binding protein to target the cells. See column 14, lines 25-33 and examples. Kunz et al disclose that the direct sustained release dosage form-binding protein or peptide conjugations may disrupt binding protein/peptide target cell recognition. Therefore, ligand sandwich attachment techniques are utilized. Such a technique involves the formation of a primary peptide or protein shell using a protein that does not bind to the target cell population. The binding protein/peptide is then bound to the primary peptide or protein shell to provide a particulate with functional binding protein/peptide. For example, the poly-lactic/glycolic acid particulates are reacted with avidin or streptavidin to form protein-coated particulates. Additionally, the binding protein/peptide may be partially entrapped in the particulate polymeric matrix upon formation of the particulate. See column 25, line 20 to column 26, line 40. Therapeutic agents such as taxol or analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Taxol is taken into the cell and stabilizes the cell from further dividing. See column 4, lines 40-45 and column 13, lines 24-27. The reference discloses that a skilled practitioner may determine the optimal and effective does and provides guidance, which allows one to judge if a therapeutically effective dosage has been reached on column 30, lines 6-20. Examples of dosages include .01 to 10 mg/kg per day. See column 29,

lines 10-15. Delivery of the active agents may be intravenous, intra-arterial (stents), or local delivery. See column 30, lines 56-65.

Kunz does not specify a dosing cycle up to six months or specify the taxol derivative paclitaxel, or specify coating the stent with the drug.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to manipulate the dosing cycle. One would be motivated to do so since Kunz teaches that effective and optimal dosing is within the skill of an ordinary artisan and provides the guidelines in finding the optimal dosing. Further, this is deemed an obvious and manipulatable parameter since it is determined by an array of factors such as severity of the disease, the patient, the drug, etc.

Further, it would have been obvious to utilize paclitaxel as the drug of choice since Kunz teaches the use of taxol or taxol analogs thereof and since paclitaxel is an analog of taxol. Therefore, one would be motivated to use paclitaxel with the expectation of similar results.

Lastly, although Kunz does not explicitly state that the drug is coated into the stent, it is implicit that the drug would be coated onto the stent since this is the standard procedure in employing biological stents.

Conclusion

All claims remain rejected at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-

242-0614. The examiner can normally be reached on M-F (8:00-5:00) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SSG

April 15, 2004

MICHAEL G. HARTLEY
PRIMARY EXAMINER